REMARKS

Claims 1-5 are pending for examination.

Correspondence Address

Applicants note that an Advisory Action was mailed to the previous address for Applicants' representatives and was returned to the P.T.O. as undeliverable. Applicants respectfully request that future correspondence be sent to the address indicated for the customer number provided below.

Inventorship

The Examiner asserts that the request for the deletion of inventors submitted in the previous Amendment and Response to Office Action filed August 13, 2004 was deficient because it was not signed by a party set forth in 37 C.F.R. §1.33(b) and does not acknowledge that the deleted inventors' invention is no longer being claimed in the instant application as required by 37 C.F.R. §1.48(b)(1).

Applicants note that the previous Amendment and Response to Office Action was signed by an Attorney of Record and that 37 C.F.R. §1.33(b)(1) lists attorneys of record as being authorized to sign such documents. In addition, Applicants note that page 5 of the previous Amendment and Response to Office Action provides that the deleted inventors' inventions are no longer being claimed as a result of prosecution.

In view of the foregoing, Applicants maintain that the request for deletion of inventors is proper.

Rejection Under 35 U.S.C. §101

The Examiner asserts that Claims 1-5 are not supported by a specific and substantial asserted utility or a well-established utility. The Examiner asserts that the Declarations stating that increased mRNA levels are predictive of increased polypeptide levels are not persuasive. The Examiner notes that the Polakis Declaration states that in 80% of the observations increases in the levels of a particular mRNA correlate with changes in the level of protein expressed from that mRNA in human tumor cells. The Examiner also notes that the Declaration of Dr. Polakis states that it remains a central dogma that increased levels of mRNA are predictive of increased levels of protein. However, the Examiner maintains that the art cited in the rejection under the

first paragaraph of 35 U.S.C. §112 discussed in more detail below supports the conclusion that mRNA over-expression does not correlate with protein over-expression.

The Examiner also asserts that the Orntoft, Hyman and Pollack references provided with the previous Amendment and Response to Office Action relate to gene amplification and do not establish that it is the norm rather than the exception that protein levels necessarily parallel gene expression in cancer cells. The Examiner cites Gokman-Polar et al. (Cancer Research, 2001 61:1375-1381) as indicating that PKC mRNA levels do not correlate with PKC protein levels.

The Examiner noted the arguments in the Ashkenazi Declaration stating that, assuming arguendo that there is no correlation between gene expression and decreased protein expression for PRO1069, an antibody to a polypeptide which is underexpressed in cancer would still have utility. However, the Examiner maintains that there is no indication that PRO1069 protein levels increase or stay the same and that further research would be required to determine PRO1069 protein levels. Accordingly, the Examiner argues that the asserted utility is not substantial because the real-world use has not been established and that the claimed utility is not specific because there is no objective evidence correlating the expression of the PRO1069 polypeptide with any particular disease state.

Applicants respectfully maintain that the claimed antibodies meet all the requirements of 35 U.S.C. §101.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must

be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test

> results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly kidney tumor. Applicants are not asserting that

the claimed antibodies necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1069 polypeptide is more highly expressed in normal kidney compared to kidney tumor;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO1069 polypeptide is decreased in kidney tumor compared to normal kidney tissue, it is likely that the PRO1069 polypeptide is differentially expressed in kidney tumors. Therefore antibodies which bind to PRO1069 are useful as a diagnostic tool to distinguish tumor from normal tissue.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO asserts that mRNA over-expression does not correlate with protein over-expression;

2. The PTO argues that the Orntoft, Hyman and Pollack references submitted with the previous Amendment and Response to Office Action relate to gene amplification and do not establish that it is the norm rather than the exception that protein levels necessarily parallel gene expression in cancer cells.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, Applicants submit that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO1069 protein is likely differentially expressed in certain tumors. This provides utility for the claimed antibodies which bind the PRO1069 polypeptide as cancer diagnostic tools. Second, Applicants submit that the Orntoft, Hyman and Pollack references show that protein levels increase with increasing copy number. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence to establish that it is **more likely than not** that a person of skill in the art would

be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not statistical or absolute certainty.**

Applicants have established that the Gene Encoding the PRO1069 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1069 polypeptide in kidney tumors is insufficient.

The gene expression data in the specification, Example 18, shows that the mRNA associated with protein PRO1069 was more highly expressed in normal kidney tissue compared to kidney tumor. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Because cDNA libraries are prepared by isolating mRNA from a particular tissue and converting it to the corresponding cDNA, the expression data in Example 18 reflect levels of mRNA in the tested tissue types. Identification of the differential expression of the PRO1069 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders antibodies which bind to the polypeptide useful as a diagnostic tool for the determination of the presence or absence of tumor. In support, Applicants previously submitted as Exhibit 1 a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are

compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1069 cDNA between kidney tumor and the normal kidney tissue. The PTO has not offered any significant arguments or evidence to the contrary. As Applicants explain below, it is more likely than not that the PRO1069 polypeptide is also differentially expressed in kidney tumor,

and can therefore be used to distinguish kidney tumor from normal kidney tissue. This provides utility for the claimed antibodies.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1069 polypeptide in kidney tumor, it is more likely than not that the PRO1069 polypeptide is differentially expressed; and antibodies which bind to proteins which are differentially expressed in certain tumors have utility as diagnostic tools.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (previously attached as Exhibit 2). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D. (previously attached as Exhibit 3), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In

> fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

Applicants submit that Mr. Grimaldi and Dr. Polakis are experts in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 1) and (4th ed. 2002) (submitted herewith as Exhibit 2)). Figure 9-2 of Exhibit 1 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 1 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 1 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 1 at 453 (emphasis added). Thus, as established in Exhibit 1, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 2, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes

according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 2 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 2 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 2 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 2 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 3) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 4. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 4 at 6. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 4 at 11. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.*

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 5, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level

> of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

With respect to the Gokman-Polar reference cited by the Examiner, the PTO relies on a statement from Gokman-Polar that "PKC mRNA levels do not directly correlate with PKC protein levels." Office Action at 4. However, a close review of the entire article indicates that with one exception, the trend in the data is that mRNA and protein levels are positively correlated, supporting Applicants assertion that increased mRNA levels correlate with increased protein levels. In Figure 2, the protein level of two isozymes shows a decrease, while the third is increased. This same pattern is seen for the corresponding mRNA levels in Figure 6, although admittedly the increase in mRNA for the third isozyme is minimal. Similarly, comparing the protein levels of the three isozymes in Figure 4 to the corresponding mRNA levels in Figure 7, with one exception the mRNA levels are positively correlated to protein levels. While protein levels do not increase or decrease in direct proportion to the changes in mRNA, the trend in five of the six examples is that protein levels are positively correlated to mRNA levels. This evidence is hardly sufficient to establish that one of skill in the art would reasonably doubt that there is a reasonable correlation between mRNA levels and protein levels.

The Examiner asserts that the Ornoft, Hyman and Pollack references provided with the previous Amendment and Response to Office Action relate to gene amplification and do not establish that it is the norm rather than the exception that protein levels necessarily parallel gene expression in cancer cells. Applicants note that Ornoft did look at mRNA and protein levels for individual genes located within amplified or deleted chromosomal regions and found that of the 40 proteins analyzed only one showed disagreement between transcript alteration and protein alteration (Ornoft, page 42). Hyman looked at the correlation between gene copy number and

mRNA levels and did not look at polypeptide levels. However, Hyman observed that "the results illustrate a considerable influence of copy number on gene expression patterns." The Pollack reference also examined the mRNA levels of individual genes within amplified regions, although polypeptide levels were not examined. Pollack concluded "that on average a 2-fold change in copy number is associated with a corresponding 1.5-fold change in mRNA levels." (Pollack, abstract). Thus, Applicants maintain that these references support the general rule that increased mRNA levels correlate with increased protein levels.

The Examiner asserts that the Ashkenazi Declaration does not establish the utility of the claimed antibodies because there is no indication that PRO1069 protein levels increase or stay the same and that further research would be required to determine PRO1069 protein levels. Applicants respectfully reiterate that regardless of whether protein levels increase or stay the same, antibodies against a polypeptide encoded by a nucleic acid differentially expressed in kidney tumors are useful for categorizing tumors and assisting the clinician in selecting an appropriate therapy. Thus, depending on the amount of polypeptide the clinician detects using the claimed antibodies, the clinician can choose whether to utilize therapies that act on the polypeptide or whether to utilize alternative approaches.

The Examiner further argues that the asserted utility is not substantial because the real-world use has not been established and that the claimed utility is not specific because there is no objective evidence correlating the expression of the PRO1069 polypeptide with any particular disease state. Applicants respectfully maintain that the diagnosis of cancer is a substantial utility. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that antibodies which bind to proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming antibodies to differentially expressed polypeptides or methods employing such antibodies. (*See, e.g.*, U.S. Patent No. 6,156,500 and U.S. Patent No. 6,562,343, attached hereto as Exhibits 6 and 7.) Thus, Applicants submit that they have established the utility of the claimed antibodies as a cancer diagnostic tool.

In view of the foregoing, Applicants submit it is more likely than not that one of skill in the art would recognize the asserted utility of the claimed antibodies as a cancer diagnostic tool.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed PR) 1069 polypeptide is differentially expressed in certain tumors and that antibodies which bind to the PRO1069 polypeptide can be used as diagnostic tools. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill

in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly kidney cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1079 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that it is more likely than not that the gene for the PRO1069 polypeptide is more highly expressed in normal kidney tissue compared to kidney tumor. These data are strong evidence that the PRO1069 gene and polypeptide are associated with kidney tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1069 gene and polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly kidney tumor, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has asserted that mRNA over-expression does not correlate with protein over-expression and that the Omtoft, Hyman and Pollack references submitted with the previous Amendment and Response to Office Action relate to gene amplification and do not establish that it is the norm rather than the exception that protein levels necessarily parallel gene expression in cancer cells.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the relative difference in expression levels, the disclosed nucleic acids and corresponding polypeptides have utility as cancer diagnostic tools. The PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration. Applicants have shown that

the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reason or evidence to question these declarations and supporting references. One of skill in the art will recognize that polypeptides differentially expressed in certain cancers have utility as diagnostic tools for cancer.

Applicants have also shown that the Orntoft, Hyman and Pollack references are consistent with the general rule that increased mRNA levels correlate with increased protein levels. Finally, Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the PRO1069 polypeptide is differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of antibodies.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies which bind to the PRO1069 polypeptide. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected Claims 1-5 on the assertion that because the claimed invention lacks utility, one skilled in the art would not know how to make and use the claimed invention. Applicants maintain that for the reasons provided above, the claimed antibodies possess utility.

The Examiner also rejected Claims 1-5 on the assertion that they encompass subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the claimed invention. In particular, the Examiner asserts that a skilled artisan would not conclude that mRNA levels are necessarily correlated with protein expression.

The Examiner cites Fu as teaching that p53 protein levels do not correlate well with levels of p53 mRNA levels, Powell as teaching that mRNA levels for cytochrome P450 did not correlate with protein levels, Vallejo as teaching no correlation between NRF-2 mRNA and protein levels, Lewin as teaching that there is no correlation between mRNA and protein levels, and Jang as teaching that further studies are necessary to determine if changes in protein levels track changes in mRNA levels for metastasis associated genes. On the basis of these references, the Examiner asserts that one skilled in the art would not accept that there is necessarily a correlation between mRNA levels and protein levels.

While these references may provide actual examples of post-transcriptional regulation of protein levels, they are not inconsistent with Applicants' position discussed above that mRNA levels correlate, more often than not, with protein levels. Applicants do not assert that post-transcriptional regulation never occurs, and furthermore need not establish that a correlation between mRNA and protein levels always exists.

Applicants respectfully submit that the great weight of the evidence supports the utility and enablement of the claimed antibodies. Applicants have provided numerous examples demonstrating a general understanding in the art that protein levels are regulated primarily by regulating mRNA levels in the large majority of cases, including the statements in Alberts, a leading textbook in the field of Molecular Biology, and the declarations of Dr. Polakis and Dr. Grimaldi, both experts in the field of Cancer Biology with numerous years of experience. Of particular significance is the fact that these references have identified the general understanding in the field, as opposed to isolated examples. In addition, the experiments testified to by Dr. Polakis show a correlation between mRNA and protein levels for a large number of different

genes. These references are in addition to the numerous examples of particular genes shown by Applicants, including those in Example 18 of the specification, and in Zhigang and Meric. Applicants respectfully submit that the totality of the above-cited evidence clearly establishes that those of skill in the art would believe that mRNA levels more likely than not correlate with protein levels.

The Examiner's citation of Vallejo, Powell, Jang and Fu as examples of particular genes for which the levels of mRNA do not correlate with the level of the corresponding proteins does not rebut this evidence, but rather provides examples of post-transcriptional modification, the existence of which is acknowledged by Applicants. Applicants note that the passage from Lewin cited by the Examiner supports Applicants' position that in general mRNA levels correlate with protein levels. In particular, the cited passage provides that "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." In light of the fact that Applicants need not show a *necessary* correlation between mRNA and protein levels, Applicants respectfully submit that they have rebutted any prima facie case of non-utility and non-enablement the Examiner may have established. In fact, the "more likely than not" standard would effectively be an "absolute certainty" standard if the Examiner's few instances of post-transcriptional regulation were found to establish the non-existence of a general correlation between mRNA and protein levels in light of the totality of evidence produced above by Applicants. Accordingly, Applicants request withdrawal of the rejection of the pending claims under 35 U.S.C. §112.

Rejections Under 35 U.S.C. §103

Claims 1-5 were rejected as being obvious over Lal (WO 00/00610) in view of Queen (U.S. Patent No. 5,530,101). In particular, the Examiner has maintained the rejection in the previous Office Action asserting that Lal discloses the polypeptide of SEQ ID NO: 50 and that Queen discloses humanized antibodies.

Applicants maintain that Lal does not constitute prior art with respect to the present application. Applicants first disclosed SEQ ID NO: 50 in U.S. Provisional Application Serial No. 60/088740, filed June 10, 1998. In contrast, Lal's first provisional application relating to SEQ ID NO: 50, U.S. Provisional Application Serial No. 60/090,762, was filed June 26, 1998

(after Applicants' first application disclosing this sequence). Lal's provisional application did not contain any data correlating SEQ ID NO: 50 any particular disease or physiological function. WO 00/00610 discloses the sequence of SEQ ID NO: 50 and provides tissue distribution data for the corresponding transcript in Table 3, but does not correlate the protein with any particular disease by showing differential expression in diseased tissue relative to normal tissue and does not provide any other physiological function for the protein. In particular, Applicants maintain that the disclosure in Table 3 that the transcript is found in urologic tissue and is present to an equivalent degree in cancer, fetal tissue and inflammation (0.333 in each category) does not provide an association between the protein and any disease or physiological function.

Thus, Applicants maintain that they were in possession of so much of the invention as is disclosed in U.S. Provisional Patent Application Serial No. 60/090,762 and WO 00/00610 prior to the filing dates of each of these applications.

The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention".

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need not be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need not have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority back to a disclosure that predates the cited reference. Because Applicants demonstrated, by means of the disclosure in their provisional application filed June 10, 1998, that they were in possession of so much of the claimed invention as is disclosed in U.S. Provisional Patent Application Serial No. 60/090,762 and WO 00/00610 prior to the filing dates of these references, Applicants respectfully submit that these references are not available as prior art.

Applicants also maintain that the disclosure of humanized antibodies in Queen does not render the claimed invention obvious since there is no teaching or suggestion of antibodies which bind the polypeptide of SEQ ID NO: 50 in Queen.

Accordingly, Applicants respectfully request that the rejection under 35 USC §103 be withdrawn.

Conclusion

The present application is believed to be in condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 14, 2005

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